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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Issued Patent No.	:	6,916,824
Issue Date	:	July 12, 2005
Appl. No.	:	09/712,612
Filing Date:	:	November 13, 2000
TC/A.U.	:	1614
Examiner	:	Fay, Zohreh A.
Applicant	:	Hua et al.
For	:	Methods of Treating Cataracts and Diabetic Retinopathy with Tricyclic Pyrones
Docket No.	:	90-99
Customer No.	:	23713

Certificate
FEB 10 2006
of Correction

Commissioner for Patents
Attention: Certificate of Corrections Branch
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING
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Cathy Nelson
Cathy Nelson

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REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. 1.322

Sir:

Please issue a Certificate of Correction for U. S. Patent 6,916,824, as errors appear in the printed patent. Enclosed are two copies of Form PTO/SB/44 with the errors listed thereon. Also enclosed are copies of the specification pages and Examiner's Amendment referred to herein.

The printing errors appeared correctly in the application, as shown by the enclosed copies of the specification pages as originally filed. Specifically, the errors in column 17, lines 35 and 39, appear correctly on page 26, lines 16 and 18 of the application as originally filed.

The error in column 30, line 42, appears correctly on page 44, line 15 of the application as originally filed.

The error in column 34, line 6, appears correctly on page 50, line 16 of the application as originally filed.

The error in Column 38, Claim 1, line 11, appears in the Examiner's Amendment received with the Notice of Allowance dated February 7, 2005.

The error in Column 38, Claim 1, line 25, appears in the Examiner's Amendment received with the Notice of Allowance dated February 7, 2005 and the Response to the Final Office Action transmitted by facsimile on December 13, 2004.

The error in Column 39, Claim 8, line 50, appears in the Examiner's Amendment received with the Notice of Allowance dated February 7, 2005.

The error in Column 40, Claim 8, line 10, appears in the Examiner's Amendment received with the Notice of Allowance dated February 7, 2005 and the Response to the Final Office Action transmitted by facsimile on December 13, 2004.

It is believed that the present submission does not require the payment of any fees. If this is incorrect however, please charge any required fee to Deposit Account No. 07-1969.

Respectfully submitted,

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February 7, 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : **6,916,824 B2**

APPLICATION NO. : **09/712,612**

ISSUE DATE : **July 12, 2005**

INVENTOR(S) : **Hua et al.**

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification:

Column 17, line 35, replace "Toirestat" with --Tolrestat--.

Column 17, line 39, replace "Toirestat" with --Tolrestat--.

Column 30, line 42, replace "diisopropylarnine" with --diisopropylamine--.

Column 34, line 6, replace "140" with --0.140--.

In the Claims:

Column 38, line 11, Claim 1, replace "damage" with --damage,--.

Column 38, line 25, Claim 1, in the first structure replace "R_a^{3}" with --R^3--.

Column 39, line 50, Claim 8, replace "retina" with --retina,--.

Column 40, line 10, Claim 8, in the first structure replace "R_a^{3}" with --R^3--.

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Human aldose reductase (AR) was obtained from overexpression of the human AR gene in an E coli system and was purified by column chromatography using a talon metal affinity column and eluted with a gradient mixture of Tris, NaCl buffer and imidazole solution. The human AR inhibition assay was conducted as follows. In a sample cuvette, 25 mM of D-xylose (75 mg/mL) and 0.15 mM of reduced nicotinamide adenine dinucleotide phosphate (NADPH) (4 mg/mL), and various amount of the inhibitor [in PBS (phosphate buffer saline) solution; the concentration of the inhibitor was determined using UV spectroscopy based on ε_{max} at λ_{max} of the drug] in 700 uL of PBS (a solution made of 1.44 g of Na_2HPO_4, 0.24 g KH_2PO_4, 0.2 g KCl, and 8 g NaCl in 1 L of distilled water) buffer (pH = 6.1) solution and 200 uL of the AR enzyme (a final volume of 1 mL was obtained). The intensity of absorption of NADPH (λ_{max} = 340 nm) was measured. When xylose is reduced to xylitol, NADPH is converted into NADP and the absorption at 340 nm decreases. When AR is inhibited by the drug, the absorption at 340 nm of NADPH remains unchanged. Each assay was repeated three times and an average IC_{50} value was obtained. Several tricyclic pyrones were tested for the inhibition of AR along with Tolrestat (obtained from Ayerst Laboratories Research, Inc., Princeton, NJ) and Sorbinil (obtained from the procedure given in *Structure* **1997**, *5*, 601-612) and the data are summarized in Table 3. Contrary to Tolrestat, compounds **1** and **2** are water soluble materials. As shown, compound **1** has greater inhibitory activity than Tolrestat and Sorbinil.

Table 3. Inhibition of Human Retina Aldose Reductase.

Inhibitor	Compound **1**	Compound **2**	Tolrestat	Sorbinil
IC_{50}	2 nM	20 nM	5 nM	2 μM

Compounds **1** and **2** (up to 100 uM) have been added to bovine lens epithelial cells and no toxicity was found.

The enzyme assay was also performed for other compounds, as shown in Table 4.

(0.29 mmol) of 3-(methoxycarbonylmethyl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]-benzopyran in a solution of 4 mL of THF and water (1:3) was added 0.033 g (0.58 mmol) of KOH at room temperature. The mixture was heated to 40°C for 14 h. It was cooled to room temperature, 30 mL of distilled water was then added, and was extracted three times with methylene chloride (40 mL each). The combined methylene chloride layer was washed with 30 mL of distilled water, and 30 mL of brine, and concentrated to give 0.021 g of starting material (26% recovery). The aqueous layer was acidified with 10 mL of 1 *N* HCl solution and extracted three times with methylene chloride (50 mL each). The combined organic layer was washed twice with distilled water (40 mL each), 40 mL of brine, dried over $MgSO_4$, concentrated to give 0.33 g of **1** (58% yield, based on recovered starting material).

5. {(5a*S*,7*S*)-7-Isopropenyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]-benzopyran-3-yl}acetic acid (6).

To a cold (-10 °C) solution of 0.27 mL (1.90 mmol) of diisopropylamine in 5 mL of diethyl ether under argon was added 1.20 mL (1.90 mmol; 1.6 M solution in hexanes) of *n*-butyllithium via syringe and the solution was stirred for 1 hour at this temperature. In another flask, 0.250 g (0.97 mmol) of **24** in 5 mL THF under argon atmosphere was prepared and cooled to -78 °C. The freshly prepared LDA was added to the above solution via cannula. The solution was allowed to react at -78°C for 2 hours. Carbon dioxide was then flushed into the solution through a balloon and insertion of a needle to allow the gas to flush out from the reaction mixture. The color of the blue anion soon changed to brownish color. The reaction mixture was stirred for 30 minutes, quenched with 10 mL saturated aqueous $NaHCO_3$, and 10 mL distilled water, and extracted with ether (15 mL x 3). The aqueous layer was acidified with 6 *N* HCl and extracted with methylene chloride (30 mL x 3). The combined methylene chloride was washed with 30 mL water, and 30 mL brine, dried over $MgSO_4$, and concentrated to give 0.271 g pure product. ^{1}H NMR δ 6.09 (s, 1 H, C4H), 5.95 (s, 1 H, C10H), 5.14 (dd, J = 11.2, 4.8 Hz, 1 H, C5aH), 4.76 (s, =CH), 4.73 (s, =CH), 3.51 (s, 2 H, CH_2), 2.50 (d, J = 14 Hz, 1 H), 2.22 ~ 2.02 (a series of m, 3 H), 1.88 ~ 1.74 (m, 2 H), 1.75 (s, 3 H, Me), 1.31 (m, 1 H).

16. (5a*S*,7*S*)-3-(Benzyloxycarbonyl)methyl-7-isopropenyl-1*H*,7*H*-5a,6,8,9-tetrahydro 1-oxopyrano[4,3-b][1]benzopyran (30)

To a cold (-10 °C) solution of 0.43 mL (3.10 mmol) of diisopropylamine in 20 mL of diethyl ether under argon was added 3.00 mL (3.10 mmol; 1.6 M solution in hexanes) of *n*-Butyl Lithium via syringe and the solution was stirred for 1 hour. In another flask, 0.400 g (1.55 mmol) of **24** in 20 mL of THF under argon was cooled to -78 °C. The freshly prepared LDA solution was added to the above solution at -78°C via cannula, then, HMPA was added to the reaction mixture via syringe and stirred at -78°C for 3 hours. To the reaction solution, 0.44 mL (3.1 mmol) of benzyl chloroformate in 20 mL THF was subsequently added to the anion solution at -78°C via cannula, and stirred for 2 more hours at this temperature. The reaction was diluted with 40 mL of distilled water and extracted three times with methylene chloride (40 mL each). The combined organic layer was washed with 40 mL of brine, dried over $MgSO_4$, concentrated, and column chromatographed through silica gel using a gradient mixture of hexane and ether to give 0.140 g of **30** (95% yield based on recovered starting material **24**) and 0.308 g (77% recovery) of **24**. **^{1}H NMR** δ 7.38 ~ 7.31 (m, 5 H, Ar), 6.08 (s, 1 H, C4H), 5.91 (s, 1 H, C10H), 5.28 (s, 2 H, CH_2OC=O), 5.12 (dd, J = 5.2 Hz, 1.2 Hz, 1 H, C5aH), 4.75 (s, 1 H, =CH_2), 4.72 (s, 1 H, =CH_2), 3.50 (s, 2 H, CH_2C=O), 2.49 ~ 2.45 (m, 1 H), 2.21 ~ 2.01 (m, 3 H), 1.86 ~ 1.70 (m, 2 H), 1.73 (s, 3 H, Me), 1.34 ~ 1.25 (m, 1 H); **^{13}C NMR** δ 167.5 (s, C=O of ester), 162.6 (s, C=O), 161.9 (s, C3), 156.2 (s, C4a), 147.8 (s, C10a), 135.2 (s, Ar), 133.2 (s, C=), 128.7 (d, Ar), 128,6 (d, Ar), 128.4 (d, Ar), 109.8 (d, C10), 109.3 (t, =CH_2), 102.2 (d, C4), 98.8 (s, C9a), 79.5 (d, C5a), 67.5 (t, OCH_2Ar), 43.4 (t, CH_2), 39.9 (d, CH), 39.4 (t, CH_2), 32.4 (t, CH_2), 31.9 (t, CH_2), 20.8 (q, Me).

17. (5a*S*,7*S*)-3-(Benzyloxycarbonyl)methyl-7-(2-hydroxy-1-methyl)ethyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (31)

A solution of 0.115 g (0.29 mmol) of **30** and 0.15 mL (0.15 mmol) of BH_3•THF complex (1.0 M in THF) in 5 mL THF was stirred for 1 h and then stored at -25°C for

Notice of Allowability	Application No. 09/712,612	Applicant(s) HUA ET AL.	
	Examiner Zohreh Fay	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendments and remarks filed on december 13, 2005*.

2. ☒ The allowed claim(s) is/are *1-7 and 24*.

3. ☒ The drawings filed on 11/13/02 are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Zohreh Fay

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Susan Doughty on February 3, 2005.

The application has been amended as follows:

The attached claims 1-7 and 24 replace claims 1-7 and 24 filed on December 13, 2004.

In claim 1 line 2 "," has been added after "damage".

In claim 24 line 3 "," has been added after "retina".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Fay whose telephone number is (571) 272-0573. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z.F